

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Pho K. Hui
Serial No: 10/667,931
Confirmation No.: 1625
Filed: September 22, 2003
For: PREPARATION OF LIPID BLEND AND A PHOSPHOLIPID
SUSPENSION CONTAINING THE LIPID BLEND
Examiner: G. S. Kishore
Art Unit: 1612

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

**DECLARATION OF MARK WATSON
UNDER 37 C.F.R. §1.132**

I, Mark Watson, declare that:

1. I am currently employed by Lantheus Medical Imaging, Inc. in the position of Senior Director, Manufacturing Technology and Development. Lantheus Medical Imaging, Inc. is the owner of the U.S. patent application having serial number: 10/667,931. My role at Lantheus includes oversight for all of Lantheus' commercial product process validation, process improvement, chemical and engineering technical support and troubleshooting. I received an MS in physical chemistry from the University of Delaware and a PhD in analytical chemistry from the University of Minnesota. I worked in product and process development for DuPont Pharmaceuticals Company and in manufacturing technology for Bristol-Myers Squibb Medical Imaging, Inc. I have over 20 years of parenteral pharmaceutical drug development experience, including substantial experience in formulation and process development and optimization. I have been closely involved in the development of manufacturing processes for a range of products for diagnostic imaging and have been extensively

involved with the development and manufacturing of the contrast imaging agent marketed in the United States as Definity®. A copy of my *Curriculum Vitae* is attached as Exhibit A.

2. I have read the above-identified patent application, the Office Action dated April 16, 2010, and the references cited therein.
3. In my positions at Lantheus Medical Imaging, Bristol-Myers Squibb Medical Imaging, and DuPont Pharmaceuticals Company, I have been extensively involved in coordinating, supervising, and analyzing procedures utilized in the manufacture of lipid blends and lipid suspensions such as, and including, those disclosed in the 10/667,931 application, which was previously owned by DuPont Pharmaceuticals Company and Bristol-Myers Squibb Medical Imaging, Inc.
4. I am aware that the 10/667,931 application describes and claims processes for preparing a lipid suspension that include steps of preparing a solution of at least two phospholipids in a non-aqueous solvent; contacting the non-aqueous lipids solution with a second non-aqueous solvent to precipitate the lipid blend; collecting the solid lipid blend; contacting the solid lipid blend with a third non-aqueous solvent to dissolve the lipid blend forming a non-aqueous lipid blend solution; and contacting the lipid blend solution with an aqueous solution to yield a lipid suspension.
5. An analysis of the data from studies performed at DuPont Pharmaceuticals Company, Bristol-Myers Squibb Medical Imaging, and Lantheus Medical Imaging confirms that performing steps (a) – (c) of claim 87 of the 10/667,931 application results in the preparation of a uniform lipid suspension after the additional steps (d) and (e) of said claim are performed. Steps (a) – (c) include dissolving at least two separate phospholipids in a non-aqueous solvent and precipitating the phospholipids from the first non-aqueous solvent by contact with a second non-aqueous solvent. Our data

indicate that the inclusion of steps (a) – (c) results in a uniform blend of the phospholipids, which can be used for manufacturing a uniform lipid suspension.

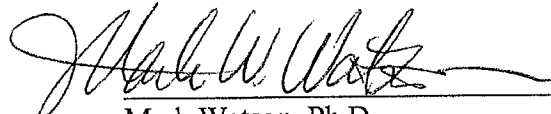
6. Our attempts to prepare lipid suspensions via addition of phospholipids to aqueous solutions did not result in a uniform distribution or particle size of the lipids and the final lipid content was highly variable. We undertook extensive additional research to develop a process that would permit manufacturing of uniform lipid suspensions. Numerous strategies were attempted including working with processes in which lipids were contacted with a non-aqueous solution followed by contact with an aqueous solution. Results of these non-aqueous to aqueous trials indicated that the lipids in the resulting suspension were not uniform in size, distribution, or yield.
7. Extensive additional experimentation was undertaken in an effort to develop an improved process that would result in a uniform lipid suspension. As a result of a substantial amount of research, we reached the unexpected finding that pre-blending of the phospholipids using a series of three non-aqueous solvents to dissolve, precipitate together, and re-dissolve the lipids, resulted in a uniform blend of the phospholipids that could be used to manufacture uniform lipid suspensions. Based on our surprising results, we were able to develop a method of pre-blending phospholipids that solved the previous difficulties of non-uniformity of lipid suspensions. The pre-blending process we developed includes steps (a) – (c) of the claim 87, and produces a lipid solution having a uniform distribution of lipids suitable for manufacturing of a lipid suspension for commercialization.
8. Other investigators have described methods to prepare liposomes including those set forth in Kissel (US Patent No. 4,863,740), Papahadjopoulos (US Patent No. 4,235,871), Lenk (US Patent No. 4,522,803), or Kikuchi (US Patent No. 4,687,661). Methods disclosed in these references are similar to our early unsuccessful strategies to prepare uniform lipid suspensions, and include dissolving lipids in a non-aqueous

solvent followed by addition of an aqueous solvent. Based on my experience working with similar methods during the development of our current process, in my opinion, a lipid suspension made using methods such as those set forth in Kissel et al., Papahadjopoulos et al., Lenk et al., or Kikuchi et al., would not have a uniform particle blend and/or uniform particle size and would not be comparable to that obtained using a process that includes the steps set forth in claim 87 of the 10/667,931 application.

9. The inclusion of steps (a) – (c) of claim 87 is critical for the preparation of the claimed lipid suspension and the resulting suspension is significantly different than a suspension that would result without inclusion of these steps. Each of the claimed steps is important to permit preparation of a uniform phospholipid blend of the claimed invention. The steps as claimed are critical to circumvent difficulties encountered using alternative methods. Such difficulties, as outlined at page 2 of the specification as filed, include lack of uniformity, lack of purity and, difficulty in recovery of solids. A process involving separate dissolution of the at least two phospholipids in a non-aqueous solvent followed by contacting said solution with an aqueous solvent would not result in the uniform suspension that we obtain using the process as claimed.
10. The lipid blend process set forth in the claims is part of the manufacturing process used for the production of Definity[®], which is the leading cardiac ultrasound contrast agent in the United States. Sales of Definity[®] in the United States in 2009 represented an approximate 92% market share. The 2009 sales of Definity[®] in Canada and Mexico represented a market share of approximately 100%. The process of steps (a) – (c) of claim 87 are critical in the manufacturing process for Definity[®], a product that is a documented commercial success both in the United States and abroad. Steps (a) – (c) and the remaining steps in claim 87, permit production of a uniform lipid suspension and is a factor in the product's commercial success.

11. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

15 Oct '10
Date


Mark Watson, Ph.D.

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OBJECTIVE

Senior level management position in small to medium size Pharmaceutical organization. Position should provide opportunities to establish and execute business and technical strategies, implement organizational change to drive improvements in efficiencies, costs and staff competencies, utilize expertise in Parenteral Product Development, Process Optimization, Technology Transfer and Product Commercialization and Life Cycle Management to influence company strategies and objectives.

QUALIFICATIONS

Over 20 years of parenteral pharmaceutical drug development experience, proven ability to organize and manage development activities associated with stability programs, formulation and process development and optimization, worldwide technology transfer, product launch and life cycle management.

Experienced in all aspects of product development from IND through NDA and product commercialization.

Knowledgeable in international regulatory filings

Comprehensive knowledge of cGMP requirements for sterile product development programs and for commercial manufacture.

Experienced with Medical Device Development and Commercialization

Proven ability to develop and manage highly effective teams in variety of organizational environments.

WORK HISTORY

Sr. Director, Manufacturing Technology and Development
2008 - present

Lantheus Medical Imaging

Responsible for updating organizational structure and membership to meet current business challenges while driving organizational and technical excellence within larger Manufacturing and Supply Chain organization.

Continue to drive continuous improvement opportunities for existing product lines and develop culture where change is valued and recognized.

Provide growth opportunities (internal and external) for staff and where necessary restructure / align organization to ensure efficient adoption of new organization expectations.

Responsible for technical elements associated with all commercial products. Areas include equipment and process validations, chemical and engineering technical support and troubleshooting, statistics and process improvements. Technical and logistical support provided for on site manufacture of 6 radiological products and off site (contract) manufacture of 7 finished products, 5 APIs and 3 devices.

Current staff: 17

Mark W. Watson

*Director, Technical Support and Development
2006 -2008*

Bristol-Myers Squibb Medical Imaging

Drive organizational and technical excellence within larger Technical Operations organization thru direct participation in key projects and initiatives.

Back integrate Operational expectations into the R&D Development programs for APIs and finished products. Ensure programs are in alignment with Corporate Best Practices and where appropriate establish effective collaborations between MI teams and corresponding HQ teams or manufacturing site teams.

Provide growth opportunities (internal and external) for staff and where necessary restructure / align organization to ensure efficient adoption of new organization expectations.

Organization is responsible for technical elements associated with all commercial products (6 hot (radiological) products, 7 cold (non-radioactive) products, 5 API's).

Total staff: 16

*Director, Manufacturing Technology
2003 -2006*

Bristol-Myers Squibb Medical Imaging

Responsible for Ultrasound Contrast Agent commercial supply strategy including process scale-up and site qualification programs.

Interface with R&D for new product technology transfer with focus on API program for pharmacological stress program.

Represent Technical Operations for novel medical device (ICT) business opportunity. Partner with R&D to establish external development partnerships to manage product development, optimization and clinical and commercial supply strategies. Program activities included world wide partnerships related to product development and optimization, manufacturing site qualification, strategy for device maintenance and worldwide commercial supply. Assembled and managed multi-disciplinary team to develop commercially viable line of products to support ICT technology.

Technical Operations representative on ICT Joint Development Team, ICT Project Team, Ultrasound Project Team and Ultrasound EU Commercialization Team.

*Senior Director, Drug Product Development
1998 - 2002*

DuPont Pharmaceuticals Company

Responsible for all aspects of Drug Product development for Medical Imaging Division. Areas of responsibility included: analytical method development and validation; formulation development and optimization; manufacturing process development, optimization and validation; technology transfer and vendor qualification. Responsibilities also include production of materials to support safety assessment and clinical studies for a variety of R&D programs.

Mark W. Watson

Senior Director, Drug Product Development ^(cont)
1998 - 2002

DuPont Pharmaceuticals Company

Responsible for all aspects of Drug Product development for Medical Imaging Division. Areas of responsibility included: analytical method development and validation; formulation development and optimization; manufacturing process development, optimization and validation; technology transfer and vendor qualification. Responsibilities also include production of materials to support safety assessment and clinical studies for a variety of R&D programs.

Responsible for formulation and process optimizations necessary to support future market growth in Ultrasound contrast Imaging. Areas of optimization included formulation improvements to increase product shelf life, process development studies to support 10x scale-up and manufacturing site technical support during product launch.

CMC representative on Radiotherapeutic and Ultrasound Project Teams

Directed group of 25 technical staff

Director, Process Development
1993-1998

DuPont Pharmaceuticals Company

Managed and directed in-house formulation and process development activities for programs associated with Pharmacologic Stress, Ultrasound Imaging and Thrombus Imaging. Responsible for pharmaceutical development sections for 4 IND submissions and 2 NDA submissions. Developed, validated and secured commercial supply of medical device required for Ultrasound agent (VIALMIX) and device for facilitating radiolabeling CARDIOLITE® (Recon-O-Stat)

Developed in-house capabilities in optical microscopy, thermal analysis and various non-destructive techniques to facilitate process development efforts.

Justified and built a cGMP aseptic manufacturing facility to support in-house production of clinical supplies, process scale-up and validation activities and technology transfers.

Promoted while in position.

Directed staff of 19 scientists.

Manager, Process Testing and Product Stability
1990-1993

DuPont Merck Pharmaceutical Company

Managed stability testing programs in support of drug development activities. Responsibilities included: technical assessment of stability profiles, justification of product specifications, ensuring protocol compliance with worldwide stability guidelines, analytical method transfers and associated ILQ's and technical support for manufacturing site pre-approval inspections. Responsible for stability sections for worldwide regulatory submissions.

Successfully interacted with Quality, Manufacturing and Regulatory Affairs in achieving objectives.

Played key role in establishing Corporate Stability Program.

Directed staff of 10 - 15 scientists

Mark W. Watson

Senior Research Chemist
1987-1990

E.I. DuPont de Nemours & Company

Responsible for analytical method development in support of pharmaceutical development programs. Provided customer training in support of product launch. CARDIOLITE® Project Leader responsible for coordinating all technical activities involved with worldwide regulatory submissions.

Research Chemist and Group Leader
1981-1987

E.I. DuPont de Nemours & Company

Responsible for analytical method development in support of agricultural product development programs. Technical supervisor for group of 6 - 10 associate scientists. Made extensive use of atomic spectroscopy, thermoanalytical methods, chromatographic methods and laboratory robotics in providing high throughput technical support to formulation and process development scientists

EDUCATION

Ph.D., Analytical Chemistry, University of Minnesota

Thesis Advisor: Dr. Peter Carr

Thesis title: "Optimization of Gradient Elution HPLC and Modification of Support Materials for High Performance Affinity Chromatography"

M.S., Physical Chemistry, University of Delaware

B.S., Chemistry, Thiel College

Professional Activities

American Chemical Society, Parenteral Drug Association and American Association of Pharmaceutical Scientists